(–)-*N*-[^{11}C]Propyl-norapomorphine [^{11}C]NPA

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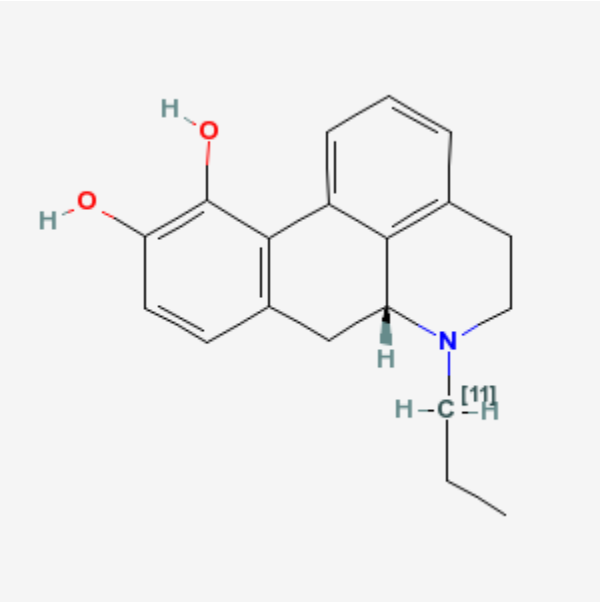
Chemical name: (–)-*N*-[^{11}C]Propyl-norapomorphine
Abbreviated name: [^{11}C]NPA
Synonym:
Backbone: Compound
Target: D_2 dopamine receptors
Mechanism: Receptor binding
Method of detection: PET
Source of signal: ^{11}C
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: No
Non-human primate studies: Yes
Human studies: No



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov].

Background

[PubMed]

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion (1, 2). Dopamine receptors are involved in the pathophysiology of neuropsychiatric diseases, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and schizophrenia (3). Five subtypes of dopamine receptors, D_1 through D_5, have been well characterized pharmacologically and biochemically (4). These five subtypes are classified into two subfamilies: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) dopamine receptors. D_1-like and D_2-like receptors exert synergistic as well as opposite effects at both the biochemical and overall system level. A great majority of striatal D_1 and D_2 receptors are localized postsynaptically on caudate-putamen neurons and to a lesser extent presynaptically on nigrostriatal axons.

Dopamine receptors are G-protein-coupled receptors and exist in high- and low-affinity states, with respect to agonist binding. The two states are interconvertible. In the high-affinity state, dopamine receptors are coupled to G-proteins, whereas the low-affinity state they are not. Dopamine has a dissociation constant (K_d) of 7 nM for the high-affinity state (K_{high}) and a K_d of 1,720 nM for the low-affinity state (K_{low}) (5). Under physiologic conditions, dopamine is expected to bind predominately to receptors in the high-affinity state. The high-affinity state was suggested to be the functional form of the dopamine receptors.

Substituted benzamides, such as sulpiride, raclopride, and iodobenzamide, are specific ligands with only moderate affinity for the D_2 receptors, making studies of extrastriatal D_2 receptors difficult (6-8). In binding studies, ^{123}I-labeled epidepride, an analog of isoremoxipride, was found to have high potency and low nonspecific binding and to be selective for striatal and extrastriatal D_2 receptors (9). Epidepride has marginal binding to D_4 receptors, with little affinity for other known neurotransmitter receptors. (S)-*N*-((1-Allyl-2-pyrrolidinyl)methyl)-5-(3-[^{18}F]fluoropropyl)-2,3-dimethoxybenzamide ([^{18}F]fallypride [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.Fallypride18F]), an analog of epidepride, was found to be a selective, high-affinity antagonist of $D_{2/3}$ receptors (10), and in positron emission tomography (PET) *in vivo* studies (11-13), it identified extrastriatal $D_{2/3}$ receptors. However, none of these antagonists distinguishes between the high- and low- affinity states of the D_2 receptors. (–)-*N*-Propyl-norapomorphine (NPA) was reported to have K_{high} and K_{low} values of 0.07-0.4 and 20-200 nM, respectively (5, 14-16). This provides a >50-fold selectivity for high-affinity over low-affinity receptors. NPA has good affinity (K_i = 0.3 nM) for D_3 receptors but not other neurotransmitters (17). [^{11}C]NPA is being developed as a PET agent for the non-invasive study of the high-affinity state of the $D_{2/3}$ receptors in the brain.

Synthesis

[PubMed]

Wong et al. (18) reported a one-pot synthesis of [^{11}C]NPA in which [^{11}C]propionyl chloride was reacted with norapomorphine followed by $LiAlH_4$ reduction, with a radiochemical yield of 16% (based on [^{11}C]CO_2 at the end of bombardment) and an average specific activity of 63 GBq/μmol (1,700 mCi/μmol at end of synthesis) after purification by C-18 Sep-Pak and high-performance liquid chromatography. Radiochemical purities were >99%. [^{11}C]Propionyl chloride was prepared by reacting [^{11}C]CO_2 with ethylmagnesium bromide, followed by reaction with phthaloyl chloride. The total synthesis time was 60 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In a binding study of dopamine receptors in membranes of the porcine anterior pituitary, [^{3}H]NPA had an average K_d of 0.26 ± 0.01 nM and a B_{max} of 2.3 ± 0.1 pmol/g tissue (19). Guanilylimidodiphosphate completely inhibited [^{3}H]NPA binding, suggesting that [^{3}H]NPA was binding primarily

to dopamine D_2 receptors in the high-affinity state. In the presence of [^{3}H]spiroperidol, NPA had K_{high} and K_{low} values of 0.27 ± 0.04 and 26 ± 2.6 nM, respectively. About 54% of D_2 receptors were in the high-affinity state. Therefore, NPA has good selectivity and affinity for the high-affinity state of D_2 receptors. George et al. (5) reported that NPA had K_{high} and K_{low} values of 0.31 and 207 nM, respectively.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in rats showed high accumulation of radioactivity in the kidney (1.00% injected dose (ID)/g), followed by the liver (0.72% ID/g), adrenal (0.66% ID/g), lung (0.31% ID/g), and spleen (0.25% ID/g) at 5 min after injection of [^{11}C]NPA (18). There was marked accumulation of the tracer in the striata within the first 30 min (0.88% ID/g), followed by a decrease of radioactivity to 0.56% ID/g at 60 min. The striatum/cerebellum and frontal cortex/cerebellum ratios were 3.47 and 1.44, respectively, at 30 min after injection. Haloperidol pretreatment (1 mg/kg) effectively blocked specific binding of [^{11}C]NPA to the striatum (from 0.88 to 0.28% ID/g) and frontal cortex (from 0.36 to 0.21% ID/g) at 30 min. Little inhibition was seen in the cerebellum (from 0.25 to 0.22% ID/g). [^{11}C]NPA thus displays uptake and wash-out kinetics characteristic of reversible radiotracers.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

[^{11}C]NPA PET studies in non-human primates have provided useful assessment of the D_2 receptor in the brain, showing localization of [^{11}C]NPA in striatal regions without agonist effects on various physiologic parameters, such as blood pressure, heart rate, respiratory rate, and body temperature (20). Wong et al (18). showed selective uptake in the striatum (0.031% ID/g) of a baboon monkey brain with striatum/cerebellum ratios of 2.33 at 15 min and 2.86 at 45 min after injection of 231 MBq (6.25 mCi) of [^{11}C]NPA. The striatal accumulation of [^{11}C]NPA was inhibited by pretreatment with haloperidol (1 mg/kg) with a striatum/cerebellum ratio of 1.29 at 45 min after injection.

Wong et al. (18) also performed quantitative measurements of [^{11}C]NPA binding with kinetic and graphical analyses, using arterial input function to derive the binding potential (BP) and specific-to-nonspecific equilibrium partition coefficient (V_3') in two baboons. In kinetic analyses, BP estimates were 4.04 ± 1.05 ml/g in the striatum, whereas BP estimates were 3.90 ± 1.03 ml/g by graphical analysis with arterial input. At 40 min post injection, 31% of [^{11}C]NPA radioactivity

remained intact in the arterial plasma. The authors concluded that data from 30 min of scanning were sufficient to derive V_3'' values by kinetic, graphical, and simplified reference-tissue model analyses.

Narendran et al. (20) studied 3 male baboons with [^{11}C]raclopride (a D_2 antagonist) and [^{11}C]NPA under baseline conditions and after administration of the potent dopamine releaser amphetamine. Kinetic modeling with an arterial input function was used to derive the striatal V_3''. The [^{11}C]raclopride V_3'' was reduced by 24 ± 10%, 32 ± 6%, and 44 ± 9% after amphetamine doses of 0.3, 0.5, and 1.0 mg/kg, respectively, whereas the [^{11}C]NPA V_3'' was reduced by 32 ± 2%, 45 ± 3%, and 53 ± 9%, respectively, after the same doses of amphetamine. Thus, endogenous dopamine was 42% more effective at competing with [^{11}C]NPA binding than [^{11}C]raclopride binding, which is consistent with the pharmacology of these tracers (agonist *versus* antagonist). These results also suggest that 71% of D_2 receptors are configured in a state of high affinity for agonists *in vivo*. [^{11}C]NPA is able to detect the change in dopamine levels induced by D-amphetamine and is more vulnerable to competition by endogenous dopamine than to competition by the antagonist radiotracer [^{11}C]raclopride. Because raclopride binds to receptors in both the high- and low-affinity states and dopamine binds with high affinity mainly to receptors in the high-affinity state, the percentage reduction is greater when an agonist is used than when an antagonist is used. This large proportion of high-affinity sites might explain the vulnerability of D_2 radiotracers to competition by endogenous dopamine and is consistent with the reported *in vivo* binding of the agonist radiotracer [^{11}C]NPA.

Narendran et al. (21) performed further PET studies in 3 baboons under non-carrier- and carrier-added conditions to compare the B_{max} values of [^{11}C]NPA and [^{11}C]raclopride in the same baboons. The [^{11}C]raclopride K_d and B_{max} were 1.59 ± 0.28 nM and 27.3 ± 3.9 nM, respectively. The *in vivo*K_d of [^{11}C]NPA was 0.16 ± 0.01 nM, consistent with its reported affinity for D_{2high}*in vitro* binding (20). The B_{max} for [^{11}C]NPA was 21.6 ± 2.8 nM and 79% of the [^{11}C]raclopride B_{max}. This result suggested that 79% of D_2 receptors are configured in the high-affinity state *in vivo*.

Human Studies

[PubMed]

No relevant publication is currently available.

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